Responses to Review Comments on Draft Report

PROPOSED RADIATION WEIGHTING FACTORS FOR USE IN
CALCULATING PROBABILITY OF CAUSATION OF CANCERS

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This discussion presents our responses to comments provided by reviewers of the draft report of October 18, 2001, entitled "Proposed Radiation Weighting Factors for Use in Calculating Probability of Causation of Cancers." These responses address technical concerns raised by the reviewers on issues of the relative biological effectiveness of different radiation types. For each reviewer in turn, a technical comment is presented, followed by our response and, as appropriate, a recommendation for modification of the draft report.

Comments of Dr. Daniel O. Stram

Comment: Dr. Stram did not provide any technical comments on the draft report. He did note, however, that "*the choices [of uncertainties in the RBE factors] ... reflect the judgment of a relatively small group of investigators (the report authors) rather than a true consensus of experts. This is probably unavoidable given the lack of good human data regarding these issues, however, the choices made here are very important, and are likely to be subject to considerable scrutiny and criticism by other experts with a different view ...*"

Response: In recognition of the judgmental nature of the choices we made in selecting probability (uncertainty) distributions of RBE factors for different radiation types, we acknowledge that better documentation of the rationale for the choices in the report is needed. This issue is addressed in responses to comments by other reviewers.

Comments of Dr. Roy E. Shore

[1]   **Comment:** "*The documentation should largely stand on its own. In this case, potentially major factors in the risk assessment (... stochastic distributions for RBE ...) are acknowledged but not explicated. These surely need to be described fully in the Final Draft.*"

Response: Without reservation, we agree that the data and judgments used to develop the subjective probability distributions of RBE factors for the different radiation types need to be fully disclosed. In all cases, the draft report provided citations to the references we used as the basis for our choices, but the report did not present the data in a way that would allow the reader to have a clear understanding of the specific information that was used and how we used that information to develop the probability distributions.

Recommendation: In revising the draft report, we intend to include tables or descriptions, as appropriate, that contain the data we used to develop the probability distributions of RBE factors. Once the data are disclosed, the reader should be able to understand the subjective judgments that are required in developing these distributions.

[2]   **Comment:** "*While it is often acknowledged that the RBE for ... x-rays is greater than unity, I have not heard of a proposed central estimate as great as 2.7 ... On Pg. 8, ... Kocher proposes the value of 2.6 (there is a discrepancy: the text says 2.6 but Table 1 says 2.7), but gives virtually a 'black box' as justification for it. There is no information given as to: 1) which data from NCRP, 1990 were used, 2) what biological endpoints were included, 3) how relevant those endpoints are to human cancer induction by radiation and a selection of the most relevant endpoints, 4) whether any evaluation of the quality of the studies that went into the estimate was made (and, for instance, only the better quality ones included), or 5) what dose ranges were used in the data from which the RBE estimate was derived. For a point as important as this one, there should be 'full disclosure' and a thorough review by knowledgable people. As it is, it cannot be meaningfully evaluated, because no data or rationale is presented.*"

Response: The thrust of this comment concerns the need for full disclosure of the basis for the choice of the probability distribution of the RBE factor for X rays. As indicated in our response to Dr. Shore's first comment, we completely agree. This response applies, for example, to the concern about which data from NCRP (1990) were used, what biological endpoints were included, and what dose ranges were used in the data from which the RBE estimate was derived.

Concerning other, more specific points in this comment, we would respond as follows. First, the apparent discrepancy between the central estimate of 2.6 given in the text and the 50th percentile of 2.7 given in Table 1 is an artifact of converting an assumed normal distribution with a central (mean) value of 2.6 and standard deviation of 0.5 to an equivalent lognormal distribution. However, we agree that such a discrepancy should be removed from the report, even though the difference has no significance.

Second, concerning the question of whether any evaluation of the quality of the studies that went into the estimate was made, our response is that we have relied greatly on reviews and evaluations of existing data by widely recognized experts in radiation biology, such as the members of the committee that prepared the NCRP report. Thus, we have depended on experts and expert groups to select high-quality studies or point out deficiencies in past studies. It was far beyond the scope of this effort to engage in a detailed and thorough review of the extensive body of primary literature relevant to issues of RBE factors. However, we also intend to augment the judgments of experts and expert groups by selected choices of relevant recent literature, as needed to support our proposed probability distributions of RBE factors.

Comments of Dr. David Richardson

Dr. Richardson offered no comments on issues of RBE factors.

Comments of Dr. Richard Hornung

Comment: "*Table 7 lists an RBE factor for alpha particles. Is this RBE for alpha to be used only for exposures to such radionuclides as plutonium or uranium? If so, you may want to footnote this at the bottom of Table 7.*"

Response: We presume that Table 7 referred to here is Table 1 in the draft report. We intend that the RBE factor for alpha particles would be applied to any exposure situations other than inhalation of short-lived alpha-emitting decay products of radon. Thus, it would be applied to exposures to any other alpha-emitting radionuclides, including plutonium and uranium.

Recommendation: We intend to modify the text and Table 1 in the draft report to indicate clearly that the RBE factor for alpha particles is to be applied to any exposures to this radiation type except inhalation of radon and its short-lived decay products.

Comments of Dr. David G. Hoel

Comment: "*With regard to the RBEs it should at least be mentioned that based on theoretical considerations, the RBEs for neutrons will likely increase with decreasing dose so things are not as simple as are mentioned in this section.*"

Response: We agree that the discussion of RBEs for neutrons, especially the discussion of how the value at low doses and dose rates, RBE_M, is determined by extrapolation of data at higher doses and dose rates, was remiss in not pointing out that RBE generally increases with decreasing dose. Indeed, this is the reason why our RBEs for neutrons at high doses and dose rates of the reference radiation are less than the values of RBE_M reported in the literature.

Recommendation: In revising the draft report, we intend to address this point by brief comments, while continuing to emphasize that the dose-dependence of RBEs for neutrons occurs mainly as a result of the non-linear dose-response relationship for the low-LET reference radiation (i.e., the dose and dose-rate effectiveness factor, DDREF, for the reference radiation is greater than one). The dose-response relationship for neutrons appears to be essentially linear and, thus, is not a substantial cause of the dose-dependence of RBE.

Comments of Dr. Robert L. Ullrich

[1]   **Comment:** "*I would ... suggest that the concept of differences in radiation interactions in small mammals versus humans (recoil protons versus gamma rays) and its impact on biological effectiveness, which is carefully stated in the first full paragraph on page 5 be moved forward in the manuscript as a general concept on page 1 paragraph 2.*"

Response: This comment refers to a discussion on the point that RBEs for neutrons obtained from studies in small mammals may overestimate the biological effectiveness of

neutrons in humans, due to the fact that a greater fraction of the dose to deep-lying organs or tissues of humans would be delivered by low-LET gamma rays. In response, we prefer to keep this discussion in the section where it appears in the draft report, mainly because the issue of differences in RBE between small mammals and humans arises only with neutrons.

Recommendation: Although we do not intend to move this discussion to the introduction to the report, we do intend to include a brief discussion in the introduction on the general question of applying data obtained from studies of different biological systems to humans. The essence of such a discussion will be that judgment is required. We also intend to expand the discussion of the issue of applying data for neutrons in small mammals to humans to indicate that the proposed probability distribution of the RBE factor for fission neutrons includes a slight bias toward lower values than are indicated by the data.

[2]   **Comment:** "*Another concern is the distribution of RBE values for neutrons in the experimental data. The authors state on page 5, lines 5 and 6, that more than 60% of the RBE values are below the arithmetic mean of 6. They state that this can be justified by different interactions between small and large animals – however a careful look at the life-shortening and tumor data suggest an alternative explanation that needs to be taken into consideration. The low RBE values for life-shortening are mainly related to studies in RF and RFM mice for which the principle cause of death and the greatest contributor to life-shortening are leukemias and lymphomas ... All of the tumor induction data suggest low RBEs for leukemias and lymphomas but higher RBE values for solid cancers – this is born out not only by the incidence data for individual tumors but also by the life-shortening data in the B6CF1 data where the causes of death are more often a result of solid tumors rather than leukemia. In all these instances neutron RBE values tend to be higher. The skewing of the RBE values to the lower end is most likely a result of a preponderance of data using RFM mice and their tendency to develop early leukemias and lymphomas rather than solid cancers.*"

Response: We appreciate this insight into the reason for the observed distribution in the observed RBEs for neutrons in studies in small mammals.

Recommendation: We now believe that, given the uncertainty in applying data on small mammals to humans, a detailed discussion of why the various measurements of RBE are distributed as they are, along the lines suggested in this comment, is not needed in the report. However, this comment also suggests that we probably placed too much emphasis on using an arithmetic mean RBE of 6, as obtained from the separate determinations in the animal studies, to define the probability distribution of RBE in humans. A better approach probably would be to select a plausible range of RBEs based on available data, make a judgment based on the data as to the form of the probability distribution (lognormal, triangular, etc.), and let the arithmetic mean fall out from this assumption. We now believe that fixing the arithmetic mean at a certain value places too much emphasis on the best estimates of the separate determinations of RBE.

[3]   **Comment:** "*Perhaps differences in RBE values for leukemia/lymphoma versus solid cancers should be considered in this report.*"

        Response: This comment was part of the longer comment discussed above. We agree that considerations of whether RBE factors for neutrons should depend on cancer type could be important. However, at this stage in the process of developing a methodology for calculating probability of causation, we believe that the approach to treating neutrons should be kept as simple as possible, and that the question raised in this comment would require a considerable amount of further study. A refinement of adopting cancer-specific RBEs could be considered if changes in the methodology were made at a later time. We also note that the probability distributions of the RBE factors for neutrons are intended to encompass the different values for leukemias and solid tumors in small mammals.

        Recommendation: In revising the draft report, we intend to note that the RBE factors for neutrons may differ for leukemia/lymphomas compared with solid tumors, but that such a refinement is not included in the methodology at the present time.

Comments of Dr. David J. Brenner

[1]   **Comment:** "*The analysis techniques ..., particularly the use of Eq. 3, are highly non standard, and are inadequately justified, particularly as there is not an established body of peer-reviewed literature to back them up. In fact the only mention of the use of Eq. 3 that I know of in the peer-reviewed literature is in a 1999 paper by Alan Edwards at the UK NRPB; Edwards discusses the advantages of the approach but finally opts for a completely different one.*"

        Response: This is one of several comments by Dr. Brenner that expressed concern about our approach to establishing RBE factors for neutrons. Our approach differs from the conventional approach of using extrapolated RBEs at low doses and dose rates, which are commonly denoted by RBE_M. In essence, because risk estimates for any radiation type are based on estimated risks at high doses and high dose rates of high-energy gamma rays in the Japanese atomic-bomb survivors, we chose to use RBE factors for neutrons that represent the biological effectiveness of these radiations relative to high acute doses of high-energy gamma rays. Since the dose-response relationship for neutrons is assumed to be linear, RBE factors for neutrons so derived apply to any dose and dose rate of neutrons, and they can be applied to risk coefficients (risks per unit dose) at high acute doses of high-energy gamma rays without adjustment for a DDREF for photons. As discussed in the draft report, this approach avoids problems (uncertainties) involved in extrapolating the available data on neutron RBEs to low doses and dose rates to obtain estimates of RBE_M.

        We acknowledge that our approach to estimating RBE factors for neutrons differs from the conventional approach of estimating these factors based on determinations of RBE_M. However, the fact that our approach has not been used widely does not negate its validity for purposes of estimating risks to human health. We believe that our approach is adequately

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justified on scientific grounds, a point that Dr. Brenner does not dispute. It also should be borne in mind that estimates of RBE_M are developed mainly for purposes of radiation protection (i.e., establishing radiation weighting factors for use in estimating equivalent doses). In support of our approach, we note that Dr. Edwards is a widely recognized expert in radiobiology whose work was used, for example, by the ICRU to develop recommendations on the quality factor for neutrons. Our approach also was endorsed by the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC), which consulted with several recognized experts in the field. Also, we showed in the draft report that our approach is consistent with the conventional use of RBE_M when the DDREF for photons normally used in radiation protection is assumed.

In regard to the comment that "Edwards discusses the advantages of the approach but finally opts for a completely different one," it does not appear to us from a reading of Edwards' paper that he opted for a different approach from the one of using RBEs obtained at high doses and dose rates of the reference radiation. As in the draft report, Edwards discusses that an appropriate RBE to be applied to estimates of risk at low doses and dose rates of photons would be twice the value of RBE obtained at high doses and dose rates if the usual assumption of a DDREF of two for the reference radiation were applied. He also discusses a recommendation by the NRPB that risks to any organ from exposure to neutrons be estimated by calculating the absorbed dose from photons and charged particles separately and applying weighting factors of 1 to the photon dose and 10 to the dose from charged particles. However, we do not see any indication in these discussions that Edwards was abandoning the approach discussed in his paper and used in the draft report.

Recommendation: We have carefully considered Dr. Brenner's comments on our approach to establishing RBE factors for neutrons. Based on these considerations and a subsequent telephone conversation with Dr. Brenner, in which he acknowledged that the approach discussed by Edwards has merit, we do not believe that the approach adopted in the draft report needs to be substantially revised or abandoned.

[2]   **Comment:** "*Nor is Eq. 3 applied uniformly, being used only for neutrons, but not for other types of radiation.*"

Response: This comment was included at the end of the longer comment discussed above. In response, there are two main reasons why the approach to risk estimation (RBE factors) embodied in eq. (3) was not used for other radiation types. First, in regard to alpha particles and beta particles from ^3H decay, most of the studies from which estimates of RBE have been obtained involved the use of reference radiations that were delivered chronically, rather than acutely, in order to match the exposure conditions for the radiation under study. Thus, in these studies, estimates of RBE at high acute doses of the reference radiation cannot be obtained. Second, an analysis similar to the one performed by Edwards to estimate RBEs for neutrons at high acute doses of the reference radiation has not, to our knowledge, been performed for alpha particles, X rays, or beta particles from ^3H decay, and it is beyond the scope of our work to undertake such an analysis. For X rays and beta particles from ^3H decay, an additional

complication that discourages the use of eq. (3) is that the reference radiation and the radiation under study both exhibit non-linear dose-response relationships, and the DDREF for the two radiations often differs substantially. The use of eq. (3) is most appropriate when the radiation under study has a linear dose-response relationship, as is the case with high-LET radiations.

Recommendation: We acknowledge that the draft report was remiss in not discussing why the method embodied in eq. (3) was not used to estimate RBE factors and cancer risks for radiation types other than neutrons. We intend to add such discussions to the sections on alpha particles and low-LET radiations.

[3]   **Comment:** "*In terms of the actual data analysis, the document relies heavily on the rather sparsely documented analysis by Edwards (1999), and almost not at all on documented primary sources. While this may be reasonable if a standard analysis technique was being used, the fact that this is not the case makes the reliance on Edwards of considerable concern. Indeed Edwards (1999) states "the values given ... result from my judgment of the basic data and other equally valid values could be obtained by others considering the same data*."

Response: In response to a comment by Dr. Shore, we noted that the probability distributions of RBE factors developed in the draft report were based primarily on reviews of the relevant literature by experts and expert groups. It was not feasible for us to undertake an independent and exhaustive investigation of the literature or an independent analysis of the available data for purposes of radiation risk assessment. In the case of neutrons, we relied on the analysis by Edwards because he is a recognized expert in the field, he analyzed a large number of experimental results, and he presented a compelling (to us) scientific case for use of the alternative approach to risk estimation embodied in eq. (3). Also, as noted previously, the approach used by Edwards was endorsed by CIRRPC.

In regard to other judgments that could be applied to the data analyzed by Edwards, we note that multiple interpretations of some data sets were included in Edwards' analysis, and that all such interpretations were included in our evaluation. Beyond that, we note only that subjective judgment is an essential aspect of deriving RBE factors for any radiation type. For virtually any data sets, different experts could arrive at somewhat different conclusions, given the uncertainties in the data. What we hope to accomplish is to provide probability (uncertainty) distributions of RBE factors that represent the preponderance of expert opinion concerning the current state of knowledge about these quantities.

Recommendation: We do not believe that this comment calls for substantive changes in the draft report. However, we will identify the sources of data that Edwards used in his analysis.

[4]   **Comment:** "*I did not find the treatment of uncertainty distributions satisfactory. In too many places parameters were simply stated without adequate justification or documentation. Again the issue of not being able to rely on past NCRP or ICRP analyses is a concern.*"

Response: The first part of this comment was addressed in the response to the first comment of Dr. Shore. Again, we agree that the report needs to properly document the sources of data we used to develop the proposed probability distributions of RBE factors.

We assume that the comment about past NCRP or ICRP analyses refers to the fact that we have not used the NCRP and ICRP recommendations on radiation weighting factors as the primary basis for selecting RBE factors. In response, we note that we did rely extensively on analyses by the NCRP and ICRP in developing our probability distributions of RBE factors. Specifically, we used the extensive reviews of data on RBEs in NCRP Report No. 104 and in ICRU Report 40, which was prepared by a Joint Task Group of the ICRU and ICRP.

We also believe it is important to emphasize that the point estimates of radiation weighting factors used by the NCRP and ICRP for purposes of radiation protection do not adequately quantify the current state of knowledge of the biological effectiveness of different types of radiation, because there clearly is substantial uncertainty in the radiobiological data from which the radiation weighting factors were derived. In the case of neutrons and alpha particles, our probability distributions of RBE factors encompass the radiation weighting factors recommended by the ICRP and NCRP. However, in the case of X rays and low-energy beta particles, the proposed probability distributions depart from the radiation weighting factors recommended by the ICRP and NCRP, because the preponderance of data does not support a conclusion that these radiations have a biological effectiveness equal to that of high-energy gamma rays. On the other hand, the proposed probability distributions for low-LET radiations are consistent, for example, with the conclusions presented in ICRU Report 40.

Recommendation: As noted previously, we intend to document the data we used to develop the probability distributions of RBE factors. In regard to the second part of this comment, we intend to include a brief discussion on the differing needs of radiation protection and radiation risk assessment and the need to base radiation risk assessments on calculational methods that take into account the state of knowledge (uncertainties) as a way of justifying departures from standard ICRP and NCRP assumptions.

[5] **Comment:** "*Because [the Draft Report of the NCI-CDC Working Group] is so grounded in the extensive prior analyses of the NCRP and ICRP, it makes for a more satisfactory basis for use in PC tables than does the report under review.*"

Response: This comment refers to the May 31, 2000, version of the "Draft Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables," which predated our draft report. In the Working Group report, the approach to estimating RBE factors, taking uncertainties into account, started with radiation weighting factors recommended by the ICRP and NCRP and applied uncertainty distributions to these point estimates. In our report, however, we took the approach of relying on the data without assuming *a priori* that the standard radiation weighting factors provided "best" estimates. The justification for our approach is contained in the response to the previous comment. We also note that more recent updates of the

draft report of the NCI-CDC Working Group have incorporated our draft report as the preferred method of establishing probability distributions of RBE factors.

Recommendation: We intend to address the issue of compatibility with ICRP and NCRP recommendations as discussed in the previous comment.

[6] **Comment:** "*The use of terminology is somewhat sloppy throughout the paper. For example the term "radiation weighting factor" (clearly defined by ICRP) is sometimes used to refer to $w_{r,L}$, and sometimes to $w_{r,H}$, this latter also sometimes being referred to as the "RBE factor.*"

Response: We agree that the use of the terms "radiation weighting factor" and "RBE factor" in the draft report to refer to the same quantity is potentially confusing and, furthermore, that the use of "radiation weighting factor" to describe the probability distributions to be used for purposes of radiation risk assessment and probability of causation probably is inappropriate, given the use of this concept by the ICRP for purposes of radiation protection.

Recommendation: In revising the draft report, we intend to abandon use of the term "radiation weighting factor" and use "RBE factor" throughout, while still making it clear that the latter term is not the same as an RBE as it is strictly defined. We also intend to change the notation (i.e., abandon the use of w_R to describe the RBE factor). However, the distinction between RBE factors at low doses and dose rates (L) and high doses and dose rates (H) is still needed and will be retained.

[7] **Comment:** "*The argument applied in rejecting use of the standard Eq. 2 relates to the question of whether high values of RBE_{max} are associated with larger values of DDREF than the factor of 2 used in analyzing low-LET A-bomb data. This may or may not be the case, but even if the authors did make a strong case, there are simpler methods to overcome the problem than rejecting the use of Eq. 2, and thus throwing away much of the accumulated analyses of the ICRP and the NCRP.*"

Response: We have addressed most of this comment in responding to previous comments by Dr. Brenner. We note here that we have not "rejected" Eq. 2 in favor of another approach. Rather, we have used an alternative, and largely consistent, approach that we believe provides better estimates of RBEs to be applied to estimated risk coefficients at high acute doses of gamma rays in the atomic-bomb survivors. Also, as noted previously, we have not "thrown away much of the accumulated analyses of the ICRP and NCRP." Rather, we have used the reviews of these organizations to elucidate the state of knowledge of RBEs, although we have not assumed *a priori* that the point estimates of radiation weighting factors represent "best" estimates of RBE factors for purposes of radiation risk assessment and probability of causation.

Recommendation: We do not believe that this comment calls for substantive revision of the draft report. We will continue to emphasize that the approaches to risk estimation for

neutrons in eqs. (2) and (3) are consistent, and that the results using eq. (3) are consistent with ICRP recommendations if a standard assumption for the DDREF is used.

[8]   **Comment:** "*The use of Eq. 3 is primarily designed to avoid problems associated with dose rate. However the authors still need to add an ad-hoc correction for inverse dose rate effects. Again this argues against changing the basic formalism used from the standard Eq. 2 to Eq. 3.*"

        Response: The use of Eq. 3 is intended to avoid problems associated with dose and dose rate. However, as discussed in the draft report and in our responses to previous comments, the problems with dose and dose rate (e.g., the dependence of RBE on dose) occur mainly as a result of the non-linear dose-response relationships for the reference radiations. The use of Eq. 3 is intended to eliminate, to some extent, the dependence of the neutron RBE on the DDREF for the reference radiation in the experimental studies. The correction for the inverse dose-rate effect is concerned only with the possible dependence of the risk on the neutron dose rate and, thus, is independent of the considerations that went into the choice to use Eq. 3.

        Recommendation: We do not believe that this comment calls for any changes in the draft report.

[9]   **Comment:** "*The argument ... that the use of Eq. 3 is necessary because the variability in the derived weighting factor [at high doses and dose rates of the reference radiation] is 'considerably less than the variability in RBE_{MAX} [at low doses and dose rates]' is weak. In the paper on which the authors relied heavily (Edwards 1999), Edwards derives a variability of a factor of 5 in derived RBE_{MAX} values, and a variability of a factor of 3⅓ in deriving $w_{R,H}$ values.*"

        Response: In the draft report, we do not argue that the use of Eq. 3 is "necessary." Rather, we argue that the approach is consistent with Eq. 2 but should provide more reliable estimates of RBE factors for neutrons to be used in conjunction with estimated risk coefficients at high acute doses of high-energy gamma rays in the atomic-bomb survivors. Indeed, we believe that the reduction in variability in the RBE factors when Eq. 3 is used is significant and illustrates the benefit of the method.

        Recommendation: Our recommendation concerning Comment [7] by Dr. Brenner applies here as well.

[10]   **Comment:** "*There are more recent data on the RBE of low-energy neutrons, published subsequent to the Edwards (1999) analysis, which should have been considered (e.g. Miller et al Int. J. Radiat. Biol. 2000). At this point the weight of evidence is probably that the cancer risk does not decrease with neutron energy from, say, 1 MeV to 50 keV ... Again, the lack of reference to primary sources is a concern here ...*"

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Response: We were aware of some of the recent literature on RBEs for neutrons, but we did not include this information unless it could affect our assumptions about probability distributions. We note that the paper by Miller et al. gives RBEs for low-energy neutrons that are in reasonable agreement with our assumed probability distribution. In response to the last statement, we reiterate that it was necessary in our work to rely on reviews of the primary sources by experts and expert groups. We generally relied on primary sources only to the extent necessary, but we agree that more recent work could be cited to support our conclusions about RBE factors.

Recommendation: In revising the draft report, we intend to continue to emphasize information obtained from reviews by experts and expert groups. However, we also intend to make note of more recent work that either supports or modifies the assumptions about probability distributions of RBE factors presented in the draft report.

[11]   **Comment:** "*The treatment of inverse dose rate effects seems inadequate and again does not seem to consider the recent literature adequately. Both theory and experiment (e.g. Lubin et al 1995) strongly suggest that the inverse dose rate effect is relevant only for protracted high doses of high-LET radiation. As the analysis nowhere uses risks or weighting factors that refer to protracted high doses of high-LET radiation, it is hard to see why Eq. 5 contains an 'enhancement factor'.*"

"*Similarly the treatment of the inverse dose-rate effect is inconsistent between neutrons and alpha particles. No rationale is given for this difference.*"

Response: In the analysis for neutrons, a small correction for a possible inverse dose-rate effect was included, based on data discussed by the NCRP, ICRP, and CIRRPC. However, this correction was not included for alpha particles based on a number of considerations, including (1) the data on exposures of underground miners to radon discussed by Lubin et al., (2) the fact that studies of the biological effectiveness of alpha particles involved protracted exposures, in which case the estimated RBEs may already include any inverse dose-rate effect, and (3) the possibility that the RBEs for alpha particles, which are extrapolated values at low doses and dose rates of the reference radiations, may be conservative when applied to humans.

We now agree that is it difficult to justify the use of a correction for the inverse dose-rate effect for neutrons but not for alpha particles. Although we believed that we could justify taking a different approach in the two cases, the available data do not provide clear evidence for or against an inverse dose-rate effect at doses of concern for either radiation type. Therefore, it would be preferable to make the same assumption for neutrons and alpha particles.

Recommendation: We intend to apply the correction for an inverse dose-rate effect for neutrons to alpha particles as well. As emphasized in the draft report, this correction is small (probably not more than a factor of 2) and our assumed probability distribution places the greatest weight on an assumption that there is no dependence of RBE on dose rate.

[12]   **Comment:** "*The use of Eq. 2 rather than Eq. 3 for photons, while welcome, makes for considerable inconsistency ... The justification ... that if one makes an 'arbitrary assumption,' the risks estimated using Eq. 3 would be about the same as the risks estimated using Eq. 2, is itself not self consistent. If one forgets about Eq. 3, however (as the authors do ...), the analysis is quite reasonable ...*"

        Response: The reasons that eq. (2) was used for photons, rather than eq. (3), are discussed in our response to Comment [2] by Dr. Brenner. What is "arbitrary" in attempting to apply eq. (3) to photons is the definition of a "high" dose, and the difficulty is that the RBE will depend on this choice when the radiation under study and the reference radiation both exhibit DDREFs that differ from unity and from each other. Our choice of 1 Gy as defining a "high" dose was used simply to show that the two methods would be compatible in this case. The comparison would have been somewhat different if a different "high" dose had been chosen. We agree, however, that the analysis involving eq. (3) for photons is not needed, especially once we have provided a proper explanation of why eq. (2) is the preferred approach for these radiations.

        Recommendation: We intend to modify the draft report along the lines indicated in the response to this comment.

[13]   **Comment:** "*Again Eq. 2 is used rather than Eq. 3, this time without any comment or discussion. It is hard to see how the authors can justify using a different risk model for neutrons compared with that for alpha particles. The only practical explanation I can see is that Edwards only produced his analysis for neutron data.*"

        Response: This comment refers to the analysis for alpha particles. In principle, neutrons and alpha particles should be handled essentially in the same way, since both are high-LET radiations. It is basically correct that we used eq. (2) for alpha particles, rather than eq. (3), because we were not aware of any analyses of RBEs at high doses and dose rates of the reference radiation, similar to the analysis by Edwards for neutrons. As discussed in responding to Comment [2] by Dr. Brenner, an additional consideration is that many studies of alpha particles used reference radiations that were delivered chronically, and these studies cannot be used to estimate RBEs at high acute doses of the reference radiation.

        Recommendation: As indicated in our response to Comment [2] by Dr. Brenner, we intend to include discussions in the draft report that explain why eq. (3) was used only for neutrons but not for any other radiation type, including alpha particles.